U.S. Pharmacopeia
The Standard of Quality℠

August 23, 1999

Dockets Management Branch
HFA 305
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

Re: Docket No. 99N-0193 "Supplements and Other Changes to an Approved Application"
✓ Docket No. 99D-0529 "Changes to an Approved NDA or ANDA"

Dear Sir or Madam:

Attached please find my testimony on behalf of the United States Pharmacopeia (USP) to the proposed rule and draft guidance relating to changes to an approved application.[1] This testimony was provided at the public meeting held by FDA on August 19, 1999.[2]

Thank you for filing these comments. Please contact me at (301) 816-8256 should you have any questions.

Sincerely,

Joseph G. Valentino
Senior Vice President and General Counsel

Attachment

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[1] 64 Fed. Reg. 34608, 34660 (June 28, 1999).

[2] 64 Fed. Reg. 42625 (Aug. 5, 1999).

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99D-0529

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Presentation

By

JOSEPH G. VALENTINO

Senior Vice President and General Counsel

United States Pharmacopeia

Changes to an Approved NDA or ANDA

August 19, 1999

Hilton Hotel, 620 Perry Parkway, Gaithersburg, MD

Sponsored by the Food and Drug Administration

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Rockville, MD 20852

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My name is Joseph G. Valentino. I am Senior Vice President and General Counsel for the United States Pharmacopeial (USP) Convention. I have been the USP designated liaison to the Food and Drug Administration (FDA), and have worked for and with the FDA for over 30 years.

The USP Convention is the publisher of the *United States Pharmacopeia* and *National Formulary (USP/NF)*. These texts and the supplements thereto are recognized as official compendia under the Federal Food, Drug & Cosmetic Act (FD&C Act). As such, their standards of strength, quality, purity, packaging, and labeling are directly enforceable under the adulteration and misbranding provisions without further approval or adoption by the FDA.

These provisions of the law are not superseded by the New Drug Provisions. The two regulatory schemes are designed to work in conjunction.

In the early nineteen eighties in order to accommodate both schemes, the USP and FDA agreed to a system by which changes by a manufacturer made in labeling and in specifications to comply with an official compendium could be made in an annual report for subsequent FDA review, rather than filing a supplement to the New Drug Application (NDA) or Abbreviated New Drug Application (ANDA) for prior approval. In return, FDA and USP would cooperate closely in the development of compendial standards.

In this manner, changes in labeling standards and regulatory methods would be applicable to all products uniformly.

The proposed regulation and guidance seek to modify the submission in the annual report to only those changes in specifications consistent with FDA requirements and that provide increased assurance that the drug will have the appropriate characteristics of identity, strength, quality, purity, and packaging.

USP believes that the proposed change can have dire effects on the regulation of drug quality and that the regulation must be made consistent with the regulatory scheme imposed by the Act.

Under § 501(b) of the FD&C Act, a drug is considered adulterated if it fails to comply with the standards of the *USP* or *NF*. If a drug differs from the official standards of strength, quality, or purity, § 501(b) provides that the difference shall be plainly stated on the product's label. Such determinations are to be made in accordance with the analytical procedures set forth in the official compendium. Of significance, the Act does not define a drug to be adulterated if it fails to meet requirements in the NDA or ANDA provisions.

The guidance and the corresponding proposed regulations require that major and moderate changes in specifications (*i.e.*, tests, analytical procedures, and acceptance criteria) be submitted to FDA in a supplemental application. Except under narrowly defined circumstances, manufacturers will no longer be able to make a change necessary to comply with the standards in the official compendia, and then submit information about that change in the annual report to the NDA or ANDA, for subsequent FDA review as provided by current regulations. However, if a standard is modified in the *USP* or *NF* and an affected product is not changed to comply with an official compendium, FDA may be obligated to consider the product as being adulterated, unless the difference is plainly stated on its label and the product is labeled NOT USP. Moreover, the product is likely also to be considered adulterated under state Food and Drug laws or under Pharmacy Acts, many of which have adopted the adulteration provisions in the FD&C Act.

According to § 501(b), FDA must bring information on "insufficient" tests or methods to the attention of the compendial body e.g, the USP. If the compendial body fails to provide sufficient tests or methods of assay, only then may FDA promulgate regulations for tests or methods of assay. Instead of notifying USP of any insufficiencies and providing USP with an opportunity to revise the current tests or develop new tests or methods of assay, FDA could, under the proposed guidance, disapprove or fail to approve the NDA or ANDA supplement containing the changed compendial method. This would result in inconsistent

regulatory methods for the same drug and would cause confusion within the industry and differences in the quality of products of the same drug in the marketplace. Other governmental bodies (Federal and State) and private sector purchasers could not rely on published compendial methods as being the regulatory method for a particular drug product, a result contrary to Congressional intent as expressed in § 501(b) of the Act.

USP revisions can result in hundreds of specification and labeling changes within any given year. The scheme proposed in the guidance allows a company to file an annual report only for minor changes made to comply with an official compendium that are consistent with "FDA requirements" and provide "the same or greater level of assurance of the identity, strength, quality, purity, or potency." These terms are vague and may even refer to confidential items unknown to the sponsor or USP in advance. Manufacturers may interpret them differently. Changes in standards of all brands of the same drug should be made simultaneously, so as to assure consistency in the market place. Implementing changes at various times, for different brands of the same drug, based on each manufacturer's interpretation of the nature of the change may cause confusion.

Differences between NDA, ANDA and compendial specifications, tests or methods of assay can create a regulatory quagmire for FDA. For example, realistically, will the agency be able to take legal action against a product failing a USP requirement, if the agency is responsible for the differing NDA specification? Conversely, will the FDA be able to hold a manufacturer to the NDA specification, when the statute indicates the USP standard or method of analysis is the comparative to be utilized? This will result in a difficult, if not untenable position for the agency. The current regulation, 21 C.F.R.§ 314.70 was adopted, in part, to prevent this from occurring.

In addition, section 502(g) of the Act provides that a drug shall be deemed misbranded unless it is labeled and packaged as prescribed in an official compendium, unless modified by the Secretary. Other sections of the Act require labeling dependent upon the compendium. For example, section 502 (e) requires labels to have the official title that appears in the *USP* or *NF*. Current 21 C.F.R.§ 314.70(c) explicitly provides that changes in

labeling made to comply with an official compendium can be submitted in an annual report. Both the guidance and the proposed regulation overlook this point entirely!

USP encourages the agency to maintain the status quo and to follow those procedures successfully implemented by FDA and USP for review of compendial revisions. These measures, which provide opportunity for FDA review of proposed compendial revisions and facilitate USP-FDA cooperation and communication, include: (l) USP's Document Disclosure Policy; (2) public notice and comment revisions in the *Pharmacopeial Forum* and the attendant Discussion Open House opportunities; (3) *USP/NF* Supplement Open House; (4) the FDA-USP ad hoc reviewers program; (5) the Joint Antibiotic subcommittee which parenthetically has recently held its 79th meeting in the past 19 years; (6) the Compendial Operations Branch; (7) liaisons to USP assigned by FDA Centers; (8) FDA review of changes in annual reports responding to compendial changes; and (9) USP-FDA high level meetings. These measures were implemented in part, as a result of the formal partnership between FDA and USP to review compendial revisions as described in the 1983 "Working Agreement Between The United States Pharmacopeial Convention, Inc. And The Food And Drug Administration" and as adapted from time to time thereafter.

USP requests that the draft guidance and regulations be modified such that:

- FDA will consider any change made in specifications to comply with an official compendium to be a minor change, reportable in an annual report and,
- FDA will consider any change made in labeling to comply with an official compendium to be a minor change, reportable in an annual report.

We believe that these changes are consistent with the regulatory scheme provided by the FD&C Act and with the procedures that USP and FDA have developed and implemented and that have worked well over the last 15 years.

Thank you.